

NATIONAL GENE VECTOR LABORATORIES

Release Date: December 1, 2000

RFA: RR-01-001

National Center for Research Resources

(<http://www.ncrr.nih.gov/>)

National Cancer Institute

(<http://www.nci.nih.gov/>)

National Institute of Diabetes and Digestive and Kidney Diseases

(<http://www.niddk.nih.gov/>)

National Institute of Arthritis and Musculoskeletal and Skin Diseases

(<http://www.nih.gov/niams/>)

National Institute of Neurological Diseases and Stroke

(<http://www.ninds.nih.gov/>)

Letter of Intent Receipt Date: January 11, 2001

Application Receipt Date: February 22, 2001

PURPOSE

The National Gene Vector Laboratories (NGVL) were established in 1995 to produce clinical grade vectors for human gene transfer protocols. The purpose of this Request for Applications (RFA) is to continue the support of the NGVL to produce and distribute such vectors and to perform related toxicology studies for Phase I and II human clinical gene transfer protocols.

For purposes of this solicitation, the term "vector" is used in the broadest sense to refer to any vehicle designed to deliver genetic material into human somatic cells for therapeutic purposes.

The National Center for Research Resources (NCRR), together with the National Cancer Institute (NCI), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Neurological Diseases and Stroke (NINDS) as co-sponsors, invite applications to join as participants in the National Gene Vector Laboratories.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic not-for-profit organizations, both public and private, such as universities, colleges, hospitals, laboratories, units of state and local governments, and eligible agencies of the Federal government. Foreign institutions are not eligible to receive awards under this solicitation. Individual members of racial and/or ethnic minority groups, women, and persons with disabilities are encouraged to apply. National Institutes of Health (NIH) policies and requirements that govern the research grant programs will apply.

MECHANISM OF SUPPORT

The administrative and funding instrument to be used for this program will be the cooperative agreement (U42), assistance mechanism rather than an acquisition mechanism, in which substantial NIH scientific and/or programmatic involvement with the awardees is anticipated during performance of the activity. Under a cooperative agreement, the NIH supports and/or stimulates the recipients' activities by working in partnership with the awardee, without assuming the direction of, prime responsibility for, or dominance in the activity. Rather, such responsibilities reside with the awardees for the project as a whole, although specific tasks and activities are shared among the awardees and the NIH Institutes and Centers (ICs). Details of the responsibilities, relationships, and governance of a study funded under a cooperative agreement are discussed later in this document under the section entitled "Terms and Conditions of the Award."

The anticipated award date is September 2001. The total project period for an application submitted in response to this RFA may not exceed five years. Although this RFA is currently anticipated to be a one-time solicitation, if it is determined that there is a sufficient, continuing need, NCRR will invite competitive new and/or competitive continuation cooperative agreement applications for review in accord with the procedures described in REVIEW CONSIDERATIONS.

FUNDS AVAILABLE

NCRR plans to commit approximately \$2 million in total costs in FY 2001 to support three to six awards in response to this RFA. These awards are to support the research infrastructure for generating both specific human gene vectors and relevant toxicology data. In addition, categorical ICs whose missions are addressed by a specific protocol can elect to support vector production and toxicology studies for that protocol.

Support for awards pursuant to this RFA will be contingent upon the quality and number of applications received and the availability of funds for this purpose. Furthermore, because the nature and scope of the activities proposed in response to this RFA will vary, it is anticipated that the size of individual awards will also vary.

RESEARCH OBJECTIVES

Background

Advances in the fields of molecular biology and genetics have led to the identification and characterization of many genes and their products. As a consequence, over 400 gene transfer clinical protocols have been initiated in the United States during the past decade. Specific gene transfer studies have addressed single gene disorders such as cystic fibrosis, severe combined immune deficiencies, hemoglobinopathies, hemophilia, and hyperlipidemia; multifactorial disorders such as cancer and heart disease; and infectious diseases such as acquired immunodeficiency syndrome (AIDS). While the promise of gene transfer was viewed as great, the technical requirements and the expense of vector development, production, and safety testing limited the capacity of clinical investigators to proceed with implementation of many protocols. Frequently, investigators had neither the ability to generate clinical grade vector in sufficient quantity nor the financial resources or time required to obtain the needed vector from commercial manufacturers. The unavailability of vector constituted a barrier to progress in the field of gene transfer.

In response to these needs, the NGVL was established as a cooperative national effort to produce and distribute vectors for human gene transfer studies. The availability of the resources provided by these facilities lowered the cost barrier posed to investigators for the production of vectors and generated vectors for rare disorders for which there was little commercial interest.

The NGVL Coordinating Center was also established in 1995 and is located at the Indiana University. It is responsible for organizing the meetings of the NGVL Review Committee and Steering Committee, receiving investigator requests for NGVL services, oversight of compliance with the NGVL Policy and Procedures document (<http://www.iupui.edu/~iucc/ngvl>), maintenance of the Toxicology Master File, post-distribution monitoring and other administrative issues. Indiana University is also the site of an existing NGVL Production Facility that generates retroviral vector.

However, additional research on development and production of such vectors is still needed and many protocols still lack an adequate supply of clinical-grade vector.

Unexpected or serious adverse events (SAEs) represent a potential danger in any clinical trial. To minimize the likelihood or seriousness of such events occurring during clinical research, toxicology studies are frequently required by the FDA before a trial is initiated. However, many grants do not provide support for such studies. In addition, toxicology data that are generated are usually considered to be proprietary and held within a Drug Master File, unavailable to other investigators. Consequently, toxicology studies are often repeated at great cost to both the research community and funding entities.

Objectives and Scope

The objective of this RFA is to expand this national infrastructure by inviting applicants to become part of the NGVL network. Awardees will then be designated either as Production Facilities to construct, produce and distribute vectors for Phase I and II human gene transfer protocols or as Toxicology Centers to generate and share toxicology data relevant to particular gene vectors for such protocols.

Through this cooperative agreement, the awardees will develop methods to produce vectors requested by clinical investigators and will assist in refining those protocols. In addition, some awardees will perform toxicology studies for NGVL-approved applications.

Quantities of clinical grade vectors, suitable for toxicology studies and sufficient for approved human gene transfer protocols will be made at the Production Facilities and distributed to investigators whose protocols have been approved by the NGVL Steering Committees and participating ICs. Highest priority for vector production will be given to projects that have peer-reviewed grant support.

Applicants seeking designation as an NGVL Production Facility must have the necessary expertise, have produced vector for human clinical trials and have established procedures and facilities that meet FDA criteria for current Good Manufacturing Practices (cGMP). They must identify the vector(s), which may include retrovirus, adenovirus, adeno-associated virus, herpesvirus, lentivirus, non-viral vectors or other types of vector that would be produced at their facility, and how they would incorporate new technologies in the future. Applicants should describe not only their capability to produce vectors for more than one protocol simultaneously,

but also their maximum production capacity, storage, safety, quality oversight and record keeping procedures.

Applicants seeking designation as Toxicology Centers within the NGVL network should document their ability to perform toxicology studies on vectors for NGVL-approved protocols. The resultant information from these studies will be maintained within NGVL databases and made accessible to the scientific community. These applicants should provide detailed information on their expertise, prior experience and facilities to conduct such animal and in vitro studies in support of human clinical trials as well as existing safety oversight and record keeping procedures. Animal facilities must be described fully and be in compliance with local, State and Federal requirements. Informatics and statistical infrastructure, procedures for transfer of data into the NGVL Toxicology Master File, quality control and quality assurance should also be addressed.

Respondents to this RFA must indicate if they are applying for an award as either a vector Production Facility or a vector Toxicology Center or both. If an institution wishes to be designated as both a vector Production Facility and Toxicology Center, two separate applications must be submitted. Each would then be reviewed on its own merits.

SPECIAL REQUIREMENTS

These cooperative agreements (U42s) will require cooperation among the NCRR Program Coordinator, the participating IC Program Officers, and the Directors of the NGVL vector Production Facilities and Toxicology Centers to maximize their effectiveness. A number of issues need to be addressed in their applications to promote the development of collaboration among the award recipients. These are discussed below.

Terms and Conditions of Award

The following terms and conditions will be incorporated into the award statement and provided to the Director of the NGVL facility as well as the institutional official at the time of award. These special Terms of Award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, HHS Grant Administration Regulations at 45 CFR Parts 74 and 92, and other HHS, PHS, and NIH Grant Administration policy statements.

The administrative and funding instrument used for this program is a cooperative agreement (U42). As described previously, the dominant role and prime responsibility for the activity resides with the awardee(s) for the project as a whole, although specific tasks and activities in carrying

out the project(s) will be shared among the awardees, the NCRR Program Coordinator and the participating IC Program Officers.

1. Awardee Rights and Responsibilities

Separate awards will be made to establish vector Production Facilities and Toxicology Centers.

Production Facilities will be responsible for generating clinical grade vectors, performing appropriate safety testing, maintaining quality control and assurance, storing and distributing vector and operating according to cGMP guidelines appropriate for Phase I and II studies.

Toxicology Centers will be responsible for conducting animal and in vitro toxicology studies that the FDA determines are needed before a particular clinical gene transfer trial can begin. They will obtain, collate, analyze and store the data generated. The data will be transmitted in the appropriate format both to the investigator for subsequent transmission to the FDA and to the NGVL Coordinating Center for inclusion in the Toxicology Master File.

Each NGVL awardee will designate a Director and Associate Director for that NGVL facility. They will then plan and design the details of the project including appropriate methods for defining and operating the facility and retaining the primary responsibility for its performance. Each NGVL facility Director must agree to participate with the NCRR Program Coordinator and the IC Program Officers as a member of the NGVL Steering Committee to provide oversight according to the NGVL Policy and Procedures document. Each Director, in cooperation with the other Steering Committee members, will be responsible for developing the details of the operating policies of the NGVL, including definition of objectives and approaches, planning, implementation, and interaction with other Directors, and assurance of scientific integrity.

The Coordinating Center Director will not only chair both the Steering Committee and Review Committee meetings but also be responsible for administration, meeting preparations, meeting agendas, writing and distributing minutes, and provide written critiques to applicants who request vector production or toxicology data of the decisions made by the NGVL. The Director of the Coordinating Center will not cast a vote on applications submitted to the Review Committee.

The Coordinating Center Director and each NGVL Facility Director must present a progress report at each meeting for incorporation into the minutes. The Steering Committee will meet at least semi-annually.

2. I/C Staff Responsibilities

One representative from the NCRR will be designated to serve as the NGVL Program Coordinator of the cooperative agreement. The NGVL Program Coordinator and one Program Officer from each co-sponsoring IC will serve on the Steering Committee in order to bring that individual's unique perspective on a given categorical disease for which the individual oversees genetic research. In consultation with the NGVL Directors, these individuals may convene workshops or sponsor seminars on advances in gene transfer accomplished through NIH support. The IC Program Officers will participate in all Steering Committee meetings and assist in developing operating policies, quality control procedures, and policies that require cooperative action. However, while the NGVL Program Coordinator and participating IC Program Officers may attend Steering Committee meetings, their cumulative votes will never exceed 40 percent.

The NGVL Program Coordinator and IC Program Officers may attend the Review Committee meetings but will not vote or express opinions that may influence the voting of the Review Committee members.

The NGVL Program Coordinator will assist in coordinating the activities of the NGVL facilities and the exchange of information. The role of the NGVL Program Coordinator and IC Program Officers, as detailed throughout these terms of cooperation, is to assist and facilitate, but not to direct activities of the NGVL. They will act as liaisons to the NIH and as information resources, bringing together groups with characterized vectors and groups with the requisite resources and expertise to implement high quality clinical gene transfer research.

3. Collaborative Responsibilities

NGVL Steering Committee

The Steering Committee coordinates and facilitates the activities supported by these cooperative agreements.

Each member of the Steering Committee will have one vote and decisions will be made on the basis of a simple majority. The total percentage of NIH representatives will not exceed 40 percent of the membership.

The members of the Steering Committee will establish the functions of the Steering Committee, its method of operation, quality control assurance, and cooperation among the NGVL Directors,

the NIH representatives, and recipients of the vectors and toxicology data generated by the facilities. The Steering Committee will also make provisions for an arbitration panel as described below. Criteria for accession and discontinuance of use of the facility will also be delineated. The Steering Committee will then reach a consensus on these issues and update the existing NGVL Policy and Procedures document. The Steering Committee will meet semi-annually at which time members will discuss these and other functional issues.

The NGVL Steering Committee will appoint outside experts to review investigators' requests for vector and toxicology support. Rules governing the selection and tenure of the members of that NGVL Review Committee will be also be established by the Steering Committee. The Directors and Associate Directors of the NGVL facilities may not attend meetings of the Review Committee. They may neither participate in the discussions nor vote nor seek to influence the decisions of the Review Committee. The Director of the NGVL Coordinating Center will chair both the Steering Committee and Review Committee meetings.

NGVL Review Committee

The Review Committee will meet semi-annually to consider applications from investigators that request production of vector or toxicology studies relevant to their protocols. This Committee will review the quality of the pre-clinical data, qualifications of the applicant and his/her institution, ethical issues, clinical protocol, consent documents and other issues outlined in the NGVL Policy and Procedures document.

Arbitration

Any disagreement that may arise between an awardee and the ICs on scientific or programmatic matters may be brought to arbitration. A panel of external consultants will be created, and convened as needed, to resolve any irreconcilable differences of opinion related to such matters. The panel will include one member selected by the NGVL Facility Directors, one member selected by the ICs, and a third member chosen by the other two members of the arbitration panel. These special arbitration procedures in no way affect an awardee's right to appeal an adverse determination in accordance with PHS regulations at 42 CFR part 50, subpart D and HHS regulations at 45 CFR part 16. Applicants should anticipate probable areas of conflict and put forward an arbitration plan in their applications.

LETTERS OF INTENT

Prospective applicants are asked to submit a letter of intent that includes a descriptive title of the proposed application, the name, address, and telephone number of the Principal Investigator, the identities of other key personnel and participating institutions, and the number and title of the RFA to which the application will respond. Although a letter of intent is neither required nor binding, and does not enter into the review of a subsequent application, its contents allow NCRR staff to estimate the potential review workload and plan the review.

The letter of intent is to be faxed, E-mailed, or mailed to John Meyer, Ph.D. at the address listed under INQUIRIES by January 11, 2001.

APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 4/98) is to be used in applying for the cooperative agreement described in this RFA. These forms are available at most institutional offices of sponsored research and from the Division of Extramural Outreach and Information Resources, National Institutes of Health, Two Rockledge Centre, 6701 Rockledge Drive, MSC 7910, Bethesda, Maryland 20892-7910, telephone 301-435-0714, email: GrantsInfo@nih.gov. Application forms are also available on the Internet at: http://grants.nih.gov/grants/funding/phs398/forms_toc.html.

Special Application Requirements

The general instructions for format, budget issues, etc., in the application packet should be followed except for the following. The Research Plan may not exceed 100 pages, and must address the issues listed below as well as points discussed in the Review Criteria section of this RFA. The budget pages of the application must address points raised below.

Applicants to this RFA should consider the points below as examples of relevant information to include in the application. These are examples only and should not be construed as being required or limiting. Applicants are encouraged to address these and/or other points pertinent to the objectives of the RFA.

1. Resources

Those responding to this RFA may apply for designation as either a vector Production Facility or a Toxicology Center or both.

A detailed description of the vector Production Facility and its compliance with current Good Manufacturing Practice as defined by the Food and Drug Administration (FDA) should be included. Documentation must be provided of the maximum number of vectors that may be produced and maintained simultaneously and per year. Access to computer facilities should be documented.

A detailed description of the facilities available to carry out toxicology studies in compliance with Good Laboratory Practices as defined by the FDA should be included. Access to animal and virology facilities as well as any necessary computer facilities should be documented.

Compliance with Federal regulations for protection of human subjects and animals must be documented. In addition, as a condition of award, an awardee must be site visited and receive a favorable assessment by an outside panel of individuals qualified to review facilities and protocols with regard to cGMP and human subjects and animal protection issues relevant to this RFA before any vector can be produced or toxicology studies are initiated for NGVL-approved applications.

For current FDA guidance related to facilities for human gene transfer, contact:

Division of Establishment Licensing
1401 Rockville Pike, HFM-205
Rockville, MD 20852-1448
Telephone: (301) 594-2049

For information about Good Manufacturing Practices refer to Title 21 of the Code of Federal Regulations (CFR), sections 210-211 and 610. Information about Good Laboratory Practices is listed in CFR Title 21, section 58.

Pertinent portions of the CFR can be ordered from:

The Government Printing Office
Superintendent of Documents
Washington, DC 20402
Telephone: (202) 783-3238

2. Scientific Expertise and Experience in Vector Production and Toxicology

Documentation of experience in vector production and expertise in virology and molecular genetics should be provided. An understanding of important trends in gene transfer research and plans for incorporation of new technologies in the future should also be documented.

Documentation should also be provided regarding which vectors will be produced along with detailed descriptions of production methodologies. Experience in producing clinical grade vectors for prior human gene transfer protocols should be detailed, accompanied by the type(s) and quantities of vector generated, the titers obtained, and the corresponding times required to attain them. Prior experience and future plans to establish and maintain master cell banks and producer cell lines should be included.

Experience with, knowledge of, and ability to adhere to, FDA guidelines for quality control and safety testing for microbial contamination, endogenous and replication-competent viruses, and other contaminants of vectors at all stages of development and maintenance, including post distribution monitoring, should be documented. Indicate whether safety tests required will be performed within or contracted outside of the proposed NGVL facility.

Methods of certification of supernatants and final products should be described and outside sources of safety testing should be identified.

Respondents applying for support as a Toxicology Center should provide information on all animal models that are available. Information on all resources and expertise in pathology and pharmacology should be provided, accompanied by a listing of toxicology studies performed over the previous 5 years in support of Investigational New Drug (IND) applications. The list may include toxicology studies for gene transfer and non-gene transfer INDs.

Since human somatic cell gene transfer involves the administration of materials of biological products, it is regulated by the Center for Biologics Evaluation and Research (CBER), FDA. IND applications are filed concerning clinical use of such products. Respondents to this RFA should convey their familiarity with such requirements for clinical, pre-clinical and animal studies.

CBER has prepared documents relevant to this RFA that include:

- o "Points to Consider in Human Somatic Cell Therapy" (1991)
- o "Points to Consider in the Production and Testing of New Drugs and

Biologicals Produced by Recombinant DNA Technology” (1985)

- o “Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals” (1987)

- o “Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use” (1987)

- o “Points to Consider in the Collection, Processing, and Testing of Ex-Vivo Activated Mononuclear Leukocytes for Administration to Humans” (1989)

Copies of Points to Consider documents are available from:

The Division of Congressional and Public Affairs

CBER

HFM-12

1401 Rockville Pike, Suite 200 N

Rockville, MD 20852-1448

Telephone: (301) 594-0830

CBER staff members are also available to respond to questions at (301) 594-0830.

3. Collaborative Abilities

The NGVL must function as a collaborative effort among the awardees, the Coordinating Center, the NCRR Program Coordinator, the IC Program Officers and the clinical investigators.

Applicants should propose detailed plans for how they will participate in the Steering Committee and other aspects of this cooperative resource. The issues of conflicts of interest should be discussed. Suggested requirements for access to, and termination of use of, the facilities should also be discussed. Issues of intellectual property and authorship of and plans for publications should be addressed. Applicants are encouraged to review the current NGVL Policy and Procedures document available at <http://www.iupui.edu/~iucc/ngvl>.

Methods should be proposed for establishing inventories of vectors, procedures for maintaining and distributing products, tracking of the status of clinical studies and material transfer agreements.

Rules for access to the NGVL resources should be proposed and the relationship between users and investigators proposing studies defined.

4. Adherence to Terms of Cooperation

Because the Terms of Cooperation discussed above will be included in all awards issued as a result of the RFA, it is critical that each applicant include specific plans on interacting with the other awardees and NIH representatives involved in this cooperative agreement, especially with regard to the sharing of laboratory and clinical resources, policies and expertise. The applicant's experience in other multi-center efforts should be described.

BUDGET AND RELATED ISSUES

In order to fully achieve the goal of this initiative, up to four vector Production Facilities and two Toxicology Centers are proposed for support. The award will provide up to \$500,000 per year in total costs to support the infrastructure of an individual facility. Categorical ICs will provide additional funding to support the production of specific vectors and related toxicology studies.

Applicants should complete the budget information as directed in the PHS 398 application form.

Budgets for personnel and infrastructure operation must be outlined with the additional, specific costs of producing and distributing a representative vector or generating and sharing toxicology studies being itemized separately. Production Facility applicants should provide a sample budget that includes costs to produce master and producer cell banks and safety testing. Toxicology Centers should provide sample budgets for each of small animal, large animal and non-human primate studies.

The Director of each NGVL Production Facility or Toxicology Center will be a member of the Steering Committee that will meet semi-annually. Travel funds for Steering Committee and other approved meetings will be provided by the NGVL Coordinating Center.

During the course of the project period, it is anticipated that technologies will improve and the proposed protocols may change. Accordingly, it is expected that the awardees will adjust their methodologies to accommodate such changes. Workshops to review new developments in the field may be organized under the auspices of the NGVL.

Applications should present five budget periods of 12 months each that provide adequate budget justification for all applicable direct and F&A costs. An estimate of personnel efforts and corresponding costs, including the principal investigators and other staff must be included.

APPLICATIONS NOT CONFORMING TO THESE GUIDELINES WILL BE CONSIDERED UNRESPONSIVE TO THIS RFA AND WILL BE RETURNED WITHOUT FURTHER REVIEW

The RFA label available in the PHS 398 (rev. 4/98) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. Line 1 should indicate whether the application is for an award as a Production Facility or as a Toxicology Center. In addition, the RFA title and number must be typed on line 2 of the face page of the application form.

Submit a signed, typewritten original of the application, including the Checklist, and two signed photocopies, in one package to:

Center for Scientific Review
National Institutes of Health
Two Rockledge Centre, Room 1040
6701 Rockledge Drive
Bethesda, MD 20892-7710
(or Bethesda, MD 20817 if express mail or courier service is used)

At the time of submission, three additional copies of the application must be sent to the Deputy Director, Office of Review, NCRR, at the address listed under INQUIRIES.

Applications must be received by February 22, 2001. If an application is received after this date it will be returned to the applicant without review.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of an application already reviewed, but such applications must include an introduction that addresses the issues raised in the previous critique.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the Center for Scientific Review and for responsiveness by NCRR. Applications that are incomplete or non-responsive will be returned to the applicant without further consideration. Applications must adhere to the page limitations and Special Application Requirements noted under the section APPLICATION PROCEDURES above to be considered responsive.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the Office of Review, NCRR in accordance with the review criteria stated below. As part of the initial merit review, all applications will receive a written critique and may undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed, assigned a priority score, and receive a second level review by the National Advisory Research Resources Council.

Review Criteria

The goals of NIH-supported research are to advance understanding of biological systems, improve the control of disease, and enhance the health of humankind. The scientific and technical merits of the proposed activities and the organizational plans for participating in the NGVL and the extent to which they address the overall goals and objectives of the RFA will be reviewed. Reviewers will be asked to provide written comments on:

- o Qualifications and experience of the applicant and staff in producing clinical grade gene vectors or generating toxicology data for these vectors.
- o Scientific plans, methods, and analyses. Are they adequately developed, well integrated, and appropriate to production of clinical grade vector and/or performance of relevant toxicology studies? Does the applicant acknowledge potential problem areas and consider alternative tactics?
- o Experience in organizing and participating in collaborative efforts in relevant arenas such as vector production, clinical trials and toxicology studies.
- o Capability to produce vectors of appropriate type and quantity within a reasonable time frame and at a reasonable cost. Is the proposed budget justified?

- o Plans for effective and synergistic cooperation and coordination among awardees, the NGVL Coordinating Center, the Steering Committee, the NGVL Program Coordinator, the IC Program Officers and the investigators who request NGVL resources.
- o Organizational attributes of the Production Facility or Toxicology Center.
- o Availability and quality of facilities and resources required for this effort, noting that this award does not provide support for construction or renovation of facilities.
- o Scientific environment in which the work would be done. Would it contribute to the probability of success? Are there unique features present?
- o Experience in addressing issues inherent in cGMP, Good Laboratory Practice, Good Clinical Practice and protection of human subjects.
- o Qualifications of the applicant and staff in providing statistical and data management laboratory database designs, data collection and database security.
- o Evidence of institutional support.
- o Experience in implementing appropriate material transfer agreements.

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

- o The adequacy of plans to include, recruit and retain both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research.
- o The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

Schedule

Letter of Intent Receipt Date: January 11, 2001
 Application Receipt Date: February 22, 2001
 Peer Review Date: May-June, 2001
 Council Review: September 13-14, 2001

Anticipated Award Date: September 2001

AWARD CRITERIA

The earliest anticipated date of award is September 1, 2001. Awards will be based primarily on the scientific merit, vector production capability and/or ability to perform required toxicology studies, programmatic priorities and availability of funds. Some consideration may also be given to geographic diversity. The award will be subject to administrative review by NCRR and the Participating ICs upon receipt of each annual non-competitive renewal application.

Termination or Modification

NCRR reserves the right to terminate or modify each NGVL award in the event of (a) failure to develop, implement or maintain functionality, (b) substantial shortfall in efficiency, data reporting, quality control, or other such major breach in either vector production or generation of appropriate toxicology data, (c) substantive changes in an agreed-upon protocol with which the ICs cannot concur, (d) ethical issues, (e) lack of compliance with cGMP guidelines, (f) significant non-compliance with other relevant Federal guidelines, or (g) failure to provide the FDA relevant vector information or data on behalf of an investigator.

INQUIRIES

Inquiries concerning this RFA are encouraged. We welcome the opportunity to clarify any issues or respond to questions from potential applicants.

Direct inquiries regarding programmatic issues to:

Richard Knazek, M.D.
Medical Officer
Clinical Research Area
National Center for Research Resources
One Rockledge Centre, Room 6030
6705 Rockledge Drive, MSC 7965
Bethesda, MD 20892-7965
Telephone: (301) 435-0792
FAX: (301) 480-3661
Email: richardk@ncrr.nih.gov

Direct inquiries regarding review issues to:

John Meyer, Ph.D.
Deputy Director, Office of Review
National Center for Research Resources
One Rockledge Centre, Room 6018
6705 Rockledge Drive, MSC 7965
Bethesda, MD 20892-7965
Telephone: (301) 435-0806
FAX: (301) 480-3660
Email: meyerj@ncrr.nih.gov

Direct inquiries regarding fiscal matters to:

Ms. Mary Niemiec
Section Grants Management Officer
Office of Grants Management
National Center for Research Resources
One Rockledge Centre, Room 6086
6705 Rockledge Drive, MSC 7965
Bethesda, MD 20892-7965
Telephone: (301) 435-0844
FAX: (301) 480-3777
Email: maryn@ncrr.nih.gov

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to all priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople/>.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the UPDATED "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," published in the NIH Guide for Grants and Contracts on August 2, 2000

(<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html>); a complete copy of the updated Guidelines are available at

http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm:

The revisions relate to NIH defined Phase III clinical trials and require: a) all applications or proposals and/or protocols to provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) all investigators to report accrual, and to conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by NIH, unless there are clear and compelling scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects"

that was published in the NIH Guide for Grants and Contracts, March 6, 1998 and is available at the following URL address:

<http://grants.nih.gov/grants/guide/notice-files/not98-024.html>.

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.333. Awards are made under authorization of the Public Health Service Act, Titles III and IV, Sections 301, 479, and 480, as amended, Public Laws 78-410 and 99-158, 42 U.S.C. 241, 287, and 287a, as amended, and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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